EXHIBIT F

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Product Liability

*46 DISCOVERING THE CAUSE OF A DRUG'S DEFECT

Drug Manufacturers Must Follow Good Manufacturing Practices When Making Their Products. When a Defective Drug Causes Injury or Death, Documents Showing How the Drug Was Made Are Key to Proving the Defendant Failed in Its Duty to Consumers

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The Federal Food, Drug, and Cosmetic Act (FDCA) provides certain minimum standards that companies must meet when manufacturing drugs. [FN1] It identifies these standards as good manufacturing practices (GMPs). [FN2]

If a company fails to comply with the GMPs, the finished products are considered adulterated or misbranded. [FN3] The act prohibits the introduction of adulterated or misbranded products into interstate commerce. [FN4] Knowledge of the GMPs can aid in establishing whether a drug is adulterated or whether the defendant manufacturer was negligent in making it. [FN5]

The FDA is charged with monitoring drug companies' manufacturing practices and with administering and enforceing the FDCA. [FN6] The act does not allow private enforcement actions because of the possibility that such actions would duplicate state law remedies. [FN7] However, an FDCA violation may serve as an element of a state products liability action. [FN8] Violation of safety regulations and statutes provides a basis for state law negligence claims. [FN9]

When a pharmaceutical company decides to market a new drug, in addition to ensuring that its proposed manufacturing procedures comply with GMPs, it must also submit its own proposed procedures for a specific drug's manufacture, including testing methods and validations of the proposed procedures and tests.

These procedures are submitted to the FDA for approval in New Drug Applications (NDAs); for generic drugs, the procedures are listed in Abbreviated New Drug Applications (ANDAs). Neither application supersedes the published GMPs, which ensures that drugs meet the act's safety requirements and have the ingredients, strength, quality, and purity that they purport to possess. [FN10]

The FDA uses the testing and validation data to determine whether a company's procedures are eligible for approval. Once procedures are approved, a company must strictly comply with them, including the testing protocols; no changes to the procedures or testing protocols without prior FDA approval are permitted.

The FDA's regulation of the manufacture of prescription drugs is generally viewed as a minimum standard. [FN11] The FDA's acceptance of submitted procedures is evidence, not conclusive proof, of the reasonableness of

the company's manufacturing practices and procedures, and the trier of fact may assign FDA approval the weight it deserves. [FN12]

FDA approval to manufacture and market a drug is contingent on the drug company's production and testing of the product according to approved procedures. Failure to fully comply with these procedures constitutes a failure to meet minimum standards and violates the approval. If the patient takes a drug as directed and experiences an injury that the drug was promoted to prevent or has suffered an unlabeled adverse event, the manufacture of the product may be relevant.

*47 In *U.S. v. Barr Laboratories, Inc.*, the initial drug testing that Barr performed in accordance with the approved GMPs found that some drugs were "out of specification" because they did not meet the specifications described in the U.S. Pharmacopeia (USP) or the ANDA. [FN13] The results occurred because of laboratory, operator, and manufacturing errors. [FN14]

Barr's laboratory testing results reporting that the batches were "out of specification" should have triggered a well-documented failure investigation to determine why the drugs did not satisfy the USP and ANDA specifications. [FN15] The FDA-approved testing and investigation procedures, which are minimal standards, require that a documented failure investigation be performed. The failure of Barr to follow the testing protocols and the failure-investigation requirements created GMP violations. [FN16]

Examples of actionable GMP violations include

- failure to have adequate laboratory facilities
- failure to employ well-qualified personnel
- unsanitary storage of materials allowing contamination
- failure to adequately clean laboratory equipment
- failure to test raw materials
- failure to maintain written procedures of production
- failure to test batch uniformity
- inadequate labeling of materials
- inadequate laboratory procedures
- inadequate record-keeping
- failure to follow the approved or established GMPs for the specific product being tested. [FN17]

GMPs are subject to interpretation and may change over time. [FN18] If the GM Ps are ambiguous, the drug company may refer to scientific literature, industry practice, and FDA letters. [FN19] But a drug company cannot rely on approved procedures if they become inadequate. [FN20]

The manufacturing process has three stages: raw materials, work in progress, and finished product. During the raw-materials stage, employees take samples of the raw materials and test the materials to confirm that they are what they purport to be. Employees then measure and weigh the raw materials in accordance with the drug recipe.

The work-in-progress stage begins once all the raw materials have been added. During this stage, the ingredients are mixed together in strict adherence to the procedures the company submitted to the FDA. Numerous sample tests are conducted during this stage to make sure the procedures are in compliance. Finally, the drug is a finished product and is stored, packaged, and labeled for shipment.

Prefiling Investigation

When a client comes to you suspecting that he or she has taken an adulterated drug, you should tell the client to save the drug, the container, and all labeling and packaging information. A laboratory must analyze the drug and test for its active pharmaceutical ingredient (API) and for strength and purity. Gas chromatography, liquid chromatography, and microbiological tests are the three most common testing methods used for analysis.

A gas chromatograph separates the chemicals and generates a graph that can become part of the documentary evidence. The graph shows the quantity of each chemical constituent and the presence of any foreign contaminants. Gas chromatographic analysis has been largely replaced by high-performance liquid chromatography, which is faster and applicable to a wide variety of chemicals and mixtures. However, the gas chromatograph is still used for certain analyses where it can provide more accurate or specific data than the liquid chromatograph.

Microbiological tests provide information on the presence of any bacteria incapable of being detected by a chromatograph. Sterility testing is essential in the case of an injectable drug.

The product's chain of custody is equally important. The FDA requires traceability of every product. Drug companies assign lot numbers to the drugs they manufacture and ship for sale. The same is true for drugs imported into the United States.

Lot numbers can be obtained either from the drug label or from the pharmacy that filled the prescription. These numbers are important because they provide the initial direction for your investigation and will lead you to the date, location, and, occasionally, time of the drug's manufacture.

Also, you can get information about a drug company through the Freedom of Information Act (FOIA). You can find out when the last FDA inspection occurred and whether the inspector noted any deficiencies by issuing a Form 483.

A Form 483 will list any violations of FDA regulations that the inspector noted and describe the company's manufacturing problems. Warning letters, more severe than the 483s, may also be *50 obtained through a FOIA request. If a warning letter was issued, find out if the problems were corrected.

Discovery

In formal discovery, you should request specific information on the manufacture of the product. You probably will be able to find substantial documentation associated with the lot in question and with the company's policies. A number of documents may contain helpful evidence of GMP violations.

Batch records. Start with a request for the specific tablet, injection, or product of concern. Request the batch records for the lot in question, as well as the lot that immediately precedes and follows it. Determine if one lot com-

prises a batch. Sometimes a product lot is composed of multiple batches. You want data on all the batches that went into the making of the lot in question.

Batch records contain a wealth of information about the production history of a specific drug. These records contain the names of people actively involved in the manufacturing process; operating procedures followed (for example, measurements, speed and time of mixing, and cleaning of equipment in preparation for a new product); relevant dates and times; and, most important, the results of sample tests.

However, the batch record is more than a recipe. It is a complete record of the manufacture of a batch of pharmaceutical product. A batch record can be up to and in some cases more than 100 pages. It contains the complete directions for making the product and the specifications of each parameter within which the process must be conducted.

For example, in the case of tablets, the batch record will contain

- the lot numbers of the raw materials used in the batch
- the initials of the person or people who weighed the raw materials
- the mixing procedure for combining the ingredients, including the temperature, time of mixing, rotor speed, and start/stop blend times (ranges will be specified for all steps such as temperature (± X degrees), time (± Y minutes), and rotor speed (± Z rpm))
- the signatures or initials of the person who performed each step and the time of day it was done
- the tests performed
- the time when samples were taken
- the test results.

When a sample is taken to the laboratory and the process continues while the test is being conducted, the results are included later as an attachment. When the test is being performed before the next step is initiated, the results are placed directly into the batch record. Delay can harm the batch, so the test is usually rapid and conducted in the plant where the batch process moves along efficiently.

The record will show the day and time the batch was prepared, the temperature and humidity in the area where it was prepared, the names of people performing the transfer from the mixer to the tableting machine, a notation of the last calibration of the tableting-machine pressures, and details of the labeling process.

When a lot number for a particular pharmaceutical product is known, the batch record for that lot can provide a wealth of information. The data is recorded electronically as well as manually; the two recordings must match. If the electronic records indicate a mixing time of 30 minutes and the written start/stop times indicate the mixing lasted 15 minutes, this indicates an error in the lot production.

Training records. Request the training records of the people involved in the manufacture and testing of the product. These records show the educational background of the testing personnel and their specific qualifications for conducting the procedures in question.

Corrective Action, Preventive Action (CAPA) records. Request CAPA records for the time period that includes the production of the questionable lot. If something happened during production that differed from approved procedures, this will be noted as a "deviation," which the company must investigate.

For example, if a batch was specified to be mixed at 70°F ± 2°F for 30 minutes ± 2 minutes and during that time the temperature increased to 78° for 5 minutes, a deviation has occurred and must be investigated before that batch can be released. Also, if a laboratory test had a specification of 95 percent to 105 percent and a result of 92.7 percent was obtained, then a deviation called an out-of-specification result has occurred and must be investigated.

The company must complete forms indicating the actions taken in the investigation. It cannot simply admit that something went wrong. The error must be investigated by root-cause analysis, the cause must be determined, and action must be taken to prevent the error from happening again. The time involved in CAPA investigations is an indication of a company's degree of efficiency.

Standard Operating Procedures (SOPs). Request the latest revisions of SOPs and the versions in operation during the relevant time period. Determine why previous SOP versions were revised, and examine the SOPs to determine their adequacy and verify that they were followed. Many of the SOPs will be referred to in the batch record; however, there are many procedures that apply to activities before and after batch production.

Documentation of internal plant construction. Documents on plant construction*52 that occurred simultaneously with the mixing of the batch in question may be important. Foreign materials from internal construction can contaminate products during construction. A trace amount of foreign material can ruin a lot or batch.

FDA inspection documents. There are three types of FDA inspections. Preapproval inspections (PAIs) are conducted before a drug is approved to ensure that the company's proposed manufacturing procedures comply with GMPs. These inspections are scheduled. The drug company tells the FDA when it is ready for inspection. These inspections are specific to the new drug. A PAI is one of the final steps in the approval process.

The FDA also conducts random periodic inspections of a company's plant throughout the year. During these inspections, a team of FDA inspectors visits the plant and inquires into what product is being manufactured at that time. The team will usually request the past two or three batch records for that product.

The FDA will also conduct inspections when a specific violation has occurred. The agency learns of these violations when a customer files a complaint. These investigations collect data on the specific violation alleged.

The FDA is also charged with inspecting the facilities of any foreign company that produces drugs imported into the United States. Foreign inspections are generally brief and hurried. The same procedures and forms are generated as in domestic inspections.

Request the results of at least the last two FDA inspections. FDA investigators are required to file Establishment Inspection Reports (EIRs) after any inspection. These contain the details of the investigator's findings, an itemization of the negative findings that are also separately described in the Form 483, a summary of the corporate structure, a report on management's comments, and general observations regarding the defendant company.

Company internal audits. If an internal audit for the time period of the lot production in question is not available, request the audits before and after the time of the lot's production. Examine these audits and compare them with the FDA inspection findings. Other documentation maybe needed; the nature of the event being investigated and the type of drug involved will determine the need for more documents.

Application Integrity Policy documents. If the FDA questions the integrity of data submitted for the purpose

of furthering an application during the review process, it may invoke the Application Integrity Policy (AIP). [FN21] Wrongful acts that may trigger invocation of the AIP include false statements, bribes, or other efforts to subvert the application-review process. If the FDA approves a company's plan for correcting the problems--such as additional review, testing and reporting requirements, or changing responsible personnel--the AIP status can be revoked. [FN22]

Witnesses

The first deposition should be of a corporate representative on the manufacturing process. Discuss the approved GMPs with the representative and establish them as industry standards. These standards are relevant to issues of reasonable care and product defect. Other potential company witnesses include the directors of quality assurance and control, manufacturing, and laboratory testing.

You will need an expert witness who is familiar with the FDA and its established GMPs for pharmaceuticals. The expert must be able to explain what GMPs are, establish them as the minimum industry standard, and point to relevant violations.

By reviewing batch records, test procedures and results, SOPs, and employee training records; an expert can determine whether the correct ingredients were used, whether they were mixed at the correct temperature and for the correct time, whether the test procedures were performed properly, and whether appropriate sanitary controls were in place.

When discussing alleged violations, the expert should be able to describe what should have been done and why, and the difference that compliance with the relevant GMPs would have made to the finished product. He or she must connect the specific GMP violation to the negligence or defect that caused injury or loss. This causation connection is as important as determining the GMP violations because irrelevant GMP violations cannot establish the prima facie case.

Once you have established FDA-approved GMPs as the industry standard through the company representative and your expert, you are ready to present these standards to the jury. The fact that the standards are FDA-approved may or may not be allowed into evidence. The FDA imprimatur would give the standards more credibility, but it may be considered irrelevant.

A defendant's noncompliance with specific FDA regulations can be evidence of negligence per se. [FN23] Even if a court refuses to instruct the jury on negligence per se, the violations should be presented as substantive evidence of the defendant's negligence.

Documented FDA violations may become relevant during cross-examination for impeachment purposes. For example, if the defendant's expert testifies to the high quality of the defendant's manufacturing process, the plaintiff could impeach his or her opinion with FDA documents showing noncompliance with FDA regulations. [FN24]

***53** GMPs are like any other industry standard, but showing that a GMP violation is relevant to a client's injury or loss can be difficult. The manufacturing of pharmaceuticals is a highly complex process. This complexity can frustrate the consumer's ability to prove negligence and causation at trial.

Evidence of GMP violations can simplify the proof of negligence or product defect by providing the jury with a standard on which to base a finding of manufacturing negligence or product defectiveness.

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[FN1]. 21 U.S.C. §§301-399a (2008); *see generally* Deborah F. Buckman, *Remedies Available for Violations of Federal Food, Drug and Cosmetic Act (FDCA)*, 25 A.L.R. Fed. 2d 431 (2008).

[FN2]. 21 U.S.C. §351.

[FN3]. 21 U.S.C. §§351 (drugs and medical devices); 342 (food); 342(f) & (g) (dietary supplements); 361(a) (cosmetics).

[FN4]. *Id.*

[FN5]. *See e.g. Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996).

[FN6]. 21 U.S.C. §371 (a).

[FN7]. *See* Buckman, *supra* n. 1, at §11.

[FN8]. *See e.g. Merrell Dow Pharms., Inc. v. Thompson*, 478 U.S. 804 (1986).

[FN9]. *See e.g. Stanton by* ***Brooks*** *v. Astra Pharm. Prods., Inc.*, 718 F.2d 553, 563-65 (3d Cir. 1983) (holding that failure to comply with FDA regulations constituted negligence per se under Pennsylvania law).

[FN10]. *See U.S. v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 564-65 (D.N.J. 2005), *order aff'd*, 427 F.3d 219 (3d Cir. 2005).

[FN11]. The preamble to 21 C.F.R. §210.1 (a) states that "the regulations set forth in this part ... contain the minimum current good manufacturing practice[s]."

[FN12]. *See e.g. Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726, 730 (D. Minn. 2005); *see also Graham by Graham v. Wyeth Labs.*, 666 F. Supp. 1483, 1490-91 (D. Kan. 1987).

[FN13]. 812 F. Supp. 458, 466 (D.N.J. 1993).

[FN14]. *Id.*

[FN15]. *Id.* at 467-68.

[FN16]. *Id.* at 474-75, 481-82, 485-86, 488-90.

[FN17]. *See e.g. id.* at 466.

[FN18]. *Id.* at 484.

[FN19]. *Lane Labs-USA, Inc.*, 324 F. Supp. 2d at 564-65; *see also U.S. v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692 (D. Md. 2001).

[FN20]. *Barr Labs, Inc.*, 812 F. Supp. at 488.

[FN21]. FDA, *AIP Procedures*, www.fda.gov/ora/compliance_ref/aip_procedures/; *see* 56 Fed. Reg. 46191 (Sept. 10, 1991).

[FN22]. FDA, *supra* n. 21 at §1-1-7.

[FN23]. *Stanton by* ***Brooks***, 718 F.2d at 563-65.

[FN24]. *See generally* Jeffrey N. Gibbs, *The Human Genome, FDA and Product Liability*, 7 Risk 267 (1996).

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